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# THIOSINAMINE:

## *A TREATMENT FOR "INOPERABLE" TUMORS AND CICATRICIAL CONTRACTURES.*

BY

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I HAVE been experimenting with thiosinamine and studying the literature in regard to it for over a year and a half, and I think I have proved that it possesses positive curative properties in causing the resolution of benign and malignant tumors and the absorption of cicatricial tissue.

So far as reported cases go, mine are the first in which it has been employed in the treatment of keloid and other neoplasms; and, though the number of my cases has been small, the results have been positive. I believe that with increasing opportunity even greater action will be demonstrated than is now apparent.

In addition to a number in which only one or two injections were made, my own cases were three of keloid, two of recurrent and "inoperable" carcinoma, and two of lupus.

It will be fairer to earlier investigators, almost exclu-

sively as to its effect on lupus, to give the results of their observations, with corroborative or other statements of my own. Then I shall call attention to the lessons to be learned from my own cases.

The substance itself is not at all a new one to chemists. It is amply described in the edition of Fownes's *Chemistry* which I studied ten years ago. Its first use in medicine was reported by von Hebra before the Second International Congress of Dermatologists, Vienna, 1892. He had experimented with it in the hope of finding in it a cure for lupus. A number of his cases were treated in a sanitarium, where they were constantly under observation, so that his description of its physiological effects is more complete than those of Van Hoorn, Keitel, Richter, Sedziak, and myself. If I fail to confirm some of his observations it may be because my opportunities for study have been more limited.

Hebra's description of the drug is excellent:

It is allylsulphocarbamide, and is made by mixing two parts of oil of (black) mustard seed, one part of absolute alcohol, and seven parts of aqua ammoniæ of the specific gravity of 0·960, warming to 104° F., and after a few hours evaporating over a water bath. The odors of mustard and ammonia disappear, and on cooling there are deposited crystals of allylsulphocarbamide, or thiosinamine The chemical class to which this belongs is shown as follows:

$$\text{Urea is } CO{<}^{NH_2}_{NH_2} \qquad \text{Thiosinamine is } CS{<}^{NHC_3H_5}_{NH_2}$$

Thus the oxygen has been replaced by sulphur in the carboxyl, and one atom of hydrogen by the allyl radicle in the amine group.

It is soluble in water, alcohol, and ether, but, like other mustard derivatives, decomposes in aqueous solution. It

occurs in small acicular crystals and has a bitter taste and a garlicky odor.

The method in which thiosinamine was used by Hebra was the hypodermic injection of a fifteen-per-cent. alcoholic solution into the muscular tissue between the shoulder blades. A fine needle was used, and the injection was made slowly and deeply. The beginning dose was from half to three quarters of a grain, and this was injected twice a week. In lupus cases the dose was increased in the third or fourth week to half or the whole of a hypodermic syringeful of a fifteen per cent. solution, equivalent to from a grain and a half to three grains of thiosinamine twice a week. These doses were as well borne as so much distilled water, but he says they always produced a visible curative effect. In a few cases he went as high as one and a half or two syringefuls with no bad effect. Keitel and Richter used a fifteen-per-cent. alcoholic solution. I have used a ten per-cent. alcoholic solution, and Van Hoorn, on the recommendation of Professor Duclaux, of Paris, has used a ten-per-cent. solution in equal parts of water and glycerin. This he found just as active and not nearly so painful as the alcoholic solution. I shall try this in future cases. This solution has the further advantage of being available for use in agar-agar cultures and the like, where the presence of alcohol would interfere.

Hebra, as has been said, rarely reached three grains; I myself have never exceeded a grain and a half; but the other observers quoted used four grains and a half as a regular full dose, beginning, of course, with smaller ones. It appears to me that we should not try to give the largest doses that will be tolerated, but rather the smallest that will produce the therapeutic effect.

In Keitel's case and in my own cases the injections were into the muscles of the arm and forearm. In his

case there was an effect which will be described; in mine there were no ill effects. The others all made the injections into the muscles of the back.

If an alcoholic solution is used there is sharp pain lasting for less than a minute. This may be somewhat diminished by pressure to diffuse the solution through the tissues.

One very soon discovers that the syringe has to be washed out with water after the use of an alcoholic solution, otherwise the leather washers on the piston become dried and loose. Hebra mentions a syringe made by Gutentag, of Paris, with a rubber piston which can be compressed and tightened by a screw. It would be ideal for this purpose.

I found, as Hebra did, that it was desirable to discontinue treatment for ten days every six weeks or two months. The others do not seem to have done so.

Bacteriological studies of thiosinamine have been reported only by Hebra and Van Hoorn. Hebra at first found that rabbits were apparently made proof against anthrax, but in a second series of experiments all the rabbits died. Van Hoorn experimented in the Hygienic Institute in Amsterdam, with the assistance of Professor Forster. He found that the presence of a small percentage of thiosinamine in a culture medium rendered ineffectual an inoculation with certain bacteria. The addition of a few drops of a ten-per-cent. solution retarded or rendered impossible the further growth of a culture; but even flooding it with thiosinamine for twenty-four hours did not kill any bacteria. I have made no personal observations upon this subject.

The physiological effects upon animals have been studied by Hebra alone. He injected three grains daily for a month into a dog weighing twenty-two pounds.

Three grains, it will be remembered, is the largest dose he ever used for a grown man. The dog remained perfectly normal, but became ravenous, and gained nine pounds in weight. He further injected into curarized animals in the laboratory of Professor von Basch doses ten or twenty times greater in proportion to weight than in man. The only effect was a slight lowering of the pulse curve, and this was evidently due to the alcohol in which the drug was dissolved.

Its physiological effect in man is in a general way that of a very mild tonic. If the subject is perfectly sound, there are no symptoms at all produced by the injections, and if there is a lesion present the reaction which may occur is local, and is not accompanied by any general symptoms. Especially, there is never any febrile movement. There is in all cases a tonic effect with an increase in weight. Thus far my own observations and those of all the others are in accord. Hebra states that absorption is very rapid, since his patients noticed a garlicky taste in the mouth within a few minutes. The same author has noted an extraordinary diuresis, the increase in the daily amount of urine being two hundred or five hundred cubic centimetres. In no case were there renal symptoms, or the presence of albumin or other pathological product in the urine. This diuresis ceases after a number of injections. He thinks it is a therapeutic action and ceases after the abnormal fluids have been eliminated. Van Hoorn and Keitel, who both used large doses, noted after several weeks' treatment the onset of nausea, headache, and lassitude. Hebra used smaller doses and I still smaller ones, and we have not had such an experience.

Richter has studied its effect on the blood in a number of cases of lupus vulgaris, lupus erythematosus, ulcer of the leg, and cicatricial stricture of the urethra. He noted

the number of white and red blood-cells, the amount of hæmoglobin, and the changes in the morphology of the histological elements of the blood. Blood examinations were made just before the injection, four hours later, and again twenty-four hours afterward. In some cases examinations were made half an hour afterward, and in eight of these cases a change in the number of leucocytes had already taken place. The blood was always obtained by pricking the finger tip and without pressure, and always at the same hour of the day. There was uniformly an immediate decrease in the number of leucocytes to one third of the normal number—viz., from about fourteen thousand down to four thousand to the cubic millimetre. But at the end of four hours the number of leucocytes had increased to normal or beyond, and in some cases there was well-marked leucocytosis which persisted for forty eight hours. There were no uniform changes in the number of red cells. The amount of hæmoglobin was regularly increased. There was no special effect upon the number of eosinophile cells, but there was a uniform increase in the number of multinuclear leucocytes or leucocytes with polymorphous nuclei.

Richter states that in its action on the blood thiosinamine belongs to the same class of substances as hemialbumose, peptone, pepsin, nuclein, pyocyanin, tuberculin, curare, urea, uric acid, and sodium urate. Löwit has shown that the intravenous injection of these substances causes an immediate leucocytolysis followed by leucocytosis. He thinks that the first effect is the cause of the second. Since it calls into the circulation new blood elements from the blood-preparing organs, it must necessarily stimulate the activity of those organs. Of course, the real cause of this leucocytolysis is still unexplained.

There has been only one accident reported from the subcutaneous use of thiosinamine. It consisted in the pro-

duction of temporary cutaneous anæsthesia, and was observed by Keitel. The patient was a robust youth with recurrent psoriasis of a papular type, and thiosinamine was used with a view to causing absorption. The injections were made at various points, and the last one into the muscles of the extensor aspect of the forearm. This was followed very shortly by complete anæsthesia of the skin supplied by the cutaneous branch of the musculospiral nerve. It could not be stated positively that the nerve had been wounded by the needle, which I think probable, and Keitel thinks the effect due to the action of the drug itself upon the nerve. Temporary motor or sensory paralysis is not altogether unknown as an effect of the hypodermic method of medication. Thus, paralysis of entire groups of muscles after hypodermics of ether have been reported by Remak, Mendel, and Brieger. Purely cutaneous anæsthesia is not nearly so common, but two cases have been reported by Falkenheimer and Möbius. The former's was the result of a hypodermic of ether and the latter's of one of a solution of antipyrine.

In all these cases the disturbance of function was only temporary. This would seem to be a slight objection to any hypodermic medication, and not particularly to the use of thiosinamine. In one of my own cases twenty-seven hypodermics of thiosinamine were administered in the left biceps at approximately the same spot without any unfavorable effect.

Its effect upon pathological conditions is that of a powerful absorptive, acting probably by increasing the activity of the lymphatic system. This effect is seen in the absorption of serous exudations, accompanied, as before stated, by marked diuresis. It is also visible in its effect upon lupus, corneal opacities, cicatrices, glandular swellings, and neoplasms. Hebra used it in a number of tu-

berculous patients who had had no recent pulmonary symptoms, and observed a return of fever after the injections. In such cases the fever is perhaps due to the absorption of encapsulated pus. In one case of his with very severe night sweats there was repeatedly a marked amelioration following the injections. This was verified by control experiments. This same absorptive effect is so active locally that in some classes of cases a latent process may be fanned into an active one. This is especially the case in its use for clearing up opacities of the cornea; if there is the slightest inflammatory condition present this will be very much aggravated, and treatment will have to be suspended. In some cases this local inflammatory reaction is of benefit. Cases have been reported in which an apparently cured osteomyelitis has started up again after the injections—a new abscess has formed, a sinus has opened, and an *old* sequestrum has been extruded. This has been followed by definitive healing, and the entire process could only be regarded as having been a beneficent one.

Its use in the treatment of lupus is of historical interest, since that was its first therapeutic application. The results obtained by Hebra, Richter, Van Hoorn, and myself are somewhat at variance. Hebra and Van Hoorn observed in practically every case a local reaction which they describe as beginning two or three hours after the injection. The diseased part becomes red and swollen, sometimes so much so as to cause fissures in the surface. There is no vesication and there is little if any serous exudation. This reaction remains undiminished for five or six hours, but at the end of twenty-four hours has entirely disappeared. Marked desquamation sometimes follows. There is never a general reaction, and especially there is no fever. There is a sensation of heat and tension in the affected part. These two authors report this reaction to have occurred in practi-

cally every lupus case, and to have been repeated without material increase of the dose after each injection. My own lupus cases have been in dispensary practice, and the patients have not been seen until forty-eight hours after the injection. So far as the patients' statements can be counted, my cases have not shown a local reaction. Richter had a comparatively large number of cases of lupus (eleven), and in only two was there any reaction, and then only with the first two or three injections. His cases, as we have seen, were under constant observation, and the doses used were large.

As to the curative action upon lupus, Van Hoorn and Hebra observed a very great effect indeed wherever the superficial area of disease was great. Ulcerations healed, and the thickened and nodular edges flattened out. No case of complete cure is reported, and where the area involved was quite small—lupus of the cheek of the size of a dime—it was hardly influenced at all. Richter has seldom seen any effect at all upon lupus. In my own cases no "reaction" has been noted, but I have uniformly seen a diminished vascularity and a softening of the edges with healing of the ulcer. I agree with the other authors quoted that local treatment is a better means of handling lupus than the use of thiosinamine.

Its therapeutic application in clearing up corneal opacities has been attended with almost perfect success in the hands of all the investigators. Hebra had a patient who, before the injections, could hardly avoid collisions with people on the street, and afterward the acuteness of vision had so increased as to enable him to tell the direction of the wind by the weather vane on the high Rathhausthurm (city hall tower) in Vienna. He and Richter report a number of such cases, and give the formulæ for vision before and after treatment, demonstrating a remarkable increase. This is to my mind of the greatest possible importance,

for we can promise almost all these patients an astonishing improvement in vision. The cases for which it is unsuitable are those in which a vestige of inflammation is still present and might be started up into fresh phlyctenulæ.

In the treatment of cicatricial contractures thiosinamine acts by causing absorption of the fibrous tissue, whether located in the skin or in deeper parts—such as tendons and ligaments; and all the authors cited report complete cures of such cases. Among these are ectropion following lupus of the cheek, partial ankylosis of the knee from lupus, and talipes equinus following an injury (burn) of the leg. One case of ectropion was so marked that the eye could not possibly be closed, the tarsal cartilage was so rarefied by pressure and traction as to be scarcely perceptible, and even the corner of the mouth was drawn up toward the eyelid. This patient was restored to a normal condition, and the skin of the cheek became soft and freely movable on the subjacent tissues. In another case of Hebra's there was such contracture following lupus of the palm that the finger nails grew into the flesh. Complete extension was possible after about twenty-five injections, no other treatment having been employed. It was this wonderful absorptive power over cicatricial tissue which suggested to my mind its use in keloid and malignant neoplasms, in which I believe I am the first investigator.

In the treatment of simple ulcers and of stricture of the urethra, Richter's half-dozen cases, with an average of eight injections, gave negative results; but I should not regard this as final. In the case of stricture of the urethra or rectum, I believe this might be a very valuable adjunct to local treatment.

Its action upon chronically enlarged glands has been observed by Hebra, and it is to cause a very rapid absorption. In syphilitic cases, on the other hand, absorption was

not effected; and he believes that this may in some cases be of diagnostic value. He and the other authors cited have not used it in the treatment of glandular swellings secondary to epithelioma or carcinoma, some of which are described below from my own experience. It has been used with success for uterine myomata.

It has been used with negative results in eczema, psoriasis, and lupus erythematosus.

A case of mine, which I wish to describe in detail, was one of keloid. A study of the action of the drug as detailed above led me to believe it the ideal non-operative treatment for these neoplasms.

The patient, Patrick M., was a mechanic, thirty-two years old. In September, 1893, his left arm was burned from shoulder to fingers. An area about four inches and a half in diameter immediately above the elbow healed by granulation, the rest being more superficial. About four months after the accident the cicatrix began to itch and burn, and very soon a hard, prominent mass had formed in the scar. When he was admitted to St. Bartholmew's Clinic, July 7, 1894, he presented a typical keloid, consisting of two areas, each of the size of a silver dollar and projecting three quarters of an inch above the surface. These were on the flexor aspect of the arm just above the bend of the elbow. The treatment consisted in hypodermic injections into the left biceps twice a week. It should be mentioned that he applied for treatment because of impaired motion at the elbow. The beginning dose was two thirds of a grain of thiosinamine, in ten-per-cent. solution in absolute alcohol, and the highest dose used was a grain and a half. These injections produced no special effect except on the neoplasm. After one or two treatments this became very much paler, and after twelve injections one portion had lost its thickening and induration. This part was then visible as apparently normal skin, but a little paler than the rest. The other area gradually changed to the appearance of normal skin. The cure was complete

after twenty-seven injections had been made. Complete use of the arm was restored, and there was no thickening or adhesion of the skin, though the cicatrices were, of course, still recognizable.

Another patient, J. E., was referred to me by Dr. Frank Hartley for treatment by this method. He had been operated upon by another surgeon for carcinoma of the inferior maxilla, and there was an "inoperable" recurrence involving the larynx, the pharynx, and the glands of the neck. Ulceration had taken place. The effect of a few injections was very apparent indeed. The induration became somewhat less, and the foul sloughing surface became cleaner. Unfortunately, he learned at this time of the existence of a faith curer and abandoned treatment. He died some three months later.

There are reserved for another paper the description of additional cases and the consideration of the selection of cases for this treatment in preference to local means.

To recapitulate: We have in thiosinamine a drug producing, when given hypodermically, no general symptoms, and even when long continued no harmful effects. It acts specifically upon certain abnormal tissues to cause their absorption or conversion into normal tissues. It is of doubtful efficacy in lupus and a variety of skin diseases. But it is of the greatest possible value in the removal of cicatricial contractures following lupus or any other cause of loss of substance. The frightful contractures from burns of the neck would yield to its action, as cases of ectropion and corneal opacity do. My own cases have shown its curative effect upon keloid, and its palliative and probably curative effect on malignant tumors.

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